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The Prevalence of Vitamin D Deficiency and Insufficiency in Adult and Adolescent Populations

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The Prevalence of Vitamin D Deficiency and Insufficiency in Adult and Adolescent Populations

Abstract

Purpose: This review will determine the prevalence of vitamin D deficiency and insufficiency in distinct adult and adolescent populations. It will also discuss some of the major causes and effects of vitamin D deficiency and insufficiency as well as present data on the benefits of consuming vitamin D.

Methods: A literature search incorporated the following databases: Medline Ovid, Evidence Based Medicine Reviews Multifile, and The Cumulative Index to Nursing and Allied Health Literature. The search phrase “vitamin D deficiency” was used to obtain journal articles and the following limits for the search were employed: English language, core clinical journals, and humans.

Results: Six articles pertaining to vitamin D deficiency and insufficiency in adults and adolescents were chosen. The methods, results, and discussions were reviewed and the validity was analyzed.

Conclusion: Vitamin D deficiency and insufficiency are very common and widespread throughout diverse adult and adolescent populations. It is important to correct for this type of deficiency because it can lead to increased bone turnover, bone loss, and fractures. Osteomalacia causing muscle weakness and osteoporosis are also common effects of low levels of vitamin D. Finally, studies have determined that consumption of vitamin D reduces the risks of: many chronic diseases, infectious diseases, cardiovascular disease, diabetes, autoimmune diseases, and certain types of cancers

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The Prevalence of Vitamin D Deficiency and Insufficiency in Adult and Adolescent Populations

By:

Sonja Skovsted

A Clinical Research Project Submitted to the Faculty of the

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Faculty Advisor: Judy Ortiz

STATEMENT OF ACCEPTANCE:

This project is hereby accepted as a requirement for completion of the degree of:

Masters of Science in Physician Assistant Studies at Pacific University School of Physician Assistant Studies on this day the seventeenth of August, 2009.

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Biography

Sonja Skovsted was born in Milwaukee, Wisconsin but moved to Boulder, Colorado when she was one year old. Sonja grew up along the Front Range but decided to travel to the sunshine state for college. She spent four years in St. Petersburg, Florida where she attended Eckerd College and received a Bachelor of Science in Biology. Sonja was a first mate and first responder for the Eckerd College Search and Rescue team. She worked alongside the Coast Guard and assisted over 300 vessels per year with first aid, towing, firefighting, searching for overdue vessels, pulling aground vessels and dewatering sinking vessels. Sonja also completed a senior thesis project in which she studied the "Size Specific Growth Rates and Age Distribution of *Gopherus polyphemus* (Gopher tortoise) on Egmont Key, Florida." After graduation Sonja moved back to Boulder and worked as an EMT for Pridemark Paramedics and in the ER as a tech at Longmont United Hospital. It was back in Boulder that Sonja met her fiancé, Robert, who is now in law school at Lewis and Clark. In her free time Sonja enjoys exercising, disc golf, volleyball, drinking wine and playing with her cat, Tawny.

Abstract

Purpose: This review will determine the prevalence of vitamin D deficiency and insufficiency in distinct adult and adolescent populations. It will also discuss some of the major causes and effects of vitamin D deficiency and insufficiency as well as present data on the benefits of consuming vitamin D.

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Keywords: vitamin D, 25-hydroxyvitamin D, sunlight, cancer, bone, autoimmune, latitude, osteoporosis, fractures, rickets

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List of Abbreviations

25(OH)D.....25-Hydroxyvitamin D

PTH..... Parathyroid hormone

BMI.....Body mass index

HAART.....Highly active antiretroviral therapy

The Prevalence of Vitamin D Deficiency and Insufficiency in Adult and Adolescent Populations

INTRODUCTION

Adequate circulating amounts of 25-hydroxyvitamin D concentrations are critical to maintain the health and function of the immune, reproductive, muscular, skeletal and integumentary system in males and females of all ages.¹ In most individuals, the majority of vitamin D is obtained from a combination of exposure to sunlight and consumption of fatty fish, fish oils and fortified food (Table 1). Ultraviolet B radiation (wavelength, 290 to 315 nm) infiltrates the skin and converts 7-dehydracholesterol to previtamin D₃, which is then converted to vitamin D₃. It is impossible to develop vitamin D₃ toxicity from sun exposure because any excess previtamin D₃ or vitamin D₃ is destroyed by the sunlight. Dietary vitamin D is absorbed through the skin and metabolized in the liver to 25-hydroxyvitamin D. 25-hydroxyvitamin D is the serum measurement taken to assess vitamin D deficiency and insufficiency. The 25-hydroxyvitamin D is then metabolized in the kidneys by an enzyme and converted into the active form 1,25-hydroxyvitamin D (Figure I).^{2,31}

The renal production of 1,25-dihydrovitamin D is regulated by plasma parathyroid hormone levels, serum calcium, and phosphorus levels. 25-hydroxyvitamin D levels are inversely associated with parathyroid hormone levels. The PTH hormone enhances the absorption of calcium and phosphorous in the intestine by increasing the production of activated vitamin D.^{2,4} The most prominent target organs for 1,25-dihydroxyvitamin D are the intestines, the kidneys, and bones. Nuclear receptors for this secosteroid hormone have also been identified

in more than 30 other tissues. Therefore it is evident that 1,25-dihydroxyvitamin D has important functions other than calcium homeostasis.¹

It is widely accepted that vitamin D status is determined by the measurement of the circulating concentration of 25(OH)D. However, the cutoff value to define low vitamin D status remains controversial. This controversy can be partially explained by the variance of vitamin D concentrations between populations in distinct geographic locations and differences in assay methodology.⁵ Currently, there is no consensus on optimal levels of 25-hydroxyvitamin D. Vitamin D deficiency is defined by most experts as a level less than 20 ng per milliliter (50 nmol per liter).^{2,6} Many cross-sectional population studies have been conducted by graphing 25-hydroxyvitamin levels in relation to PTH. As the 25(OH)D reaches 30-40 ng per milliliter (75 to 100 nmol/l) the parathyroid hormone begins to level off. This inflection is the rationale used to identify vitamin D insufficiency. The increased secretion of PTH resulting from vitamin D insufficiency is well documented and contributes to bone fragility, fractures, and increased bone turnover. Vitamin D insufficiency is not well defined and the term is sometimes used interchangeably with deficiency. In general, a level of 21-29 ng per milliliter (52-72 nmol per liter) indicates insufficiency, and a level of 30 ng per milliliter or greater indicates a sufficient level of vitamin D.^{2,7,8}

Using the definitions above, researchers estimate that there are 1 billion people worldwide that suffer from vitamin D insufficiency or deficiency. According to several studies, 40-100% of elderly men and women, still living in the community (not in nursing homes), within the United States and Europe, have deficient levels of vitamin D.² Other studies have shown that adults and adolescents are also at potentially high risk to develop vitamin D deficiency. Even in

areas of prevalent sunshine (Arizona, Florida, Saudi Arabia and Australia) it has been documented that vitamin D deficiency and insufficiency is common.^{4,5,9,10}

The variety of effects of low levels of vitamin D have been documented and studied extensively over the past 20 years. Vitamin D deficiency or insufficiency prevents children from attaining their genetically programmed peak bone mass, contributes to and exacerbates osteoporosis in adults, and causes the often painful bone disease osteomalacia. Long-term vitamin D deficiency or insufficiency can cause: secondary hypothyroidism, increased bone turnover and bone loss, fractures, osteoarthritis and decreased muscle strength.^{2,11} Studies have also shown that consumption of vitamin D reduces your risk of developing many chronic diseases, infectious diseases, cardiovascular disease, diabetes, autoimmune diseases and certain types of cancers.^{1,2, 3,8}

Many scientific studies have been conducted and reviewed on the subject of vitamin D deficiency and insufficiency in a geriatric population (over sixty years of age) and in neonates, infants, and children. However, there are minimal studies available on a population older than nine years of age and younger than fifty years of age. Because adequate levels of vitamin D are extremely important in our everyday lives, this review will determine the prevalence of vitamin D deficiency and insufficiency in distinct adult and adolescent populations. It will also discuss some of the major causes and effects of vitamin D deficiency and insufficiency as well as present data on the benefits of consuming vitamin D.

METHODS

A literature search, incorporating several different databases, was used to find accurate and recent data on vitamin D deficiency. The search phrase “vitamin D deficiency” was utilized to obtain journal articles from the *Medline-Ovid* database. The following limits for the search were employed: “English language,” “core clinical journals,” and “humans.” A separate search within the *Evidence Based Medicine Reviews Multifile* database was also used with search phrase “vitamin D deficiency” and limits of “humans” and “English language.” The *Cumulative Index to Nursing and Allied Health Literature* database was used to search for articles with the same search phrases and limits as the other databases.

After numerous articles were located, the journal references were noted and pertinent articles were obtained via E-Journals through Pacific Universities’ library. If the article could not be obtained through the E-Journals, articles were requested through Pacific’s interlibrary loan service. After finding a sufficient quantity of articles they were read and reviewed. Three articles pertaining to adults and three articles pertaining to adolescents were chosen for analysis and review.

RESULTS

“Vitamin D insufficiency among free-living healthy young adults” by Tangpricha et al. in *The American Journal of Medicine*, 2002;112: 659-662.⁸

Purpose: To examine the high prevalence of vitamin D insufficiency in a group of free-living healthy young adults, consisting of mostly health care professionals in Boston, Massachusetts.

Methods: This study takes place in Boston, Massachusetts where the latitude is 42°N. Hospital employees, attending physicians, house staff physicians, medical students, and hospital visitors were recruited during the vitamin D awareness screening program at Boston University Medical center between March and April (end of winter) and between September and October (end of summer). Subjects were excluded if they had a history of intestinal malabsorption and were divided into four groups based on age; 18-29, 30-39, 40-49, and ≥ 50 . A questionnaire was also given to individuals to assess their intake of food and supplements containing vitamin D. An unpaired Student t-test was used to compare mean 25-hydroxyvitamin D and intact parathyroid hormone levels between groups. Chi-squared tests were used to calculate differences in proportion of vitamin D insufficiency defined as 25(OH)D level ≤ 20 ng/ml (50 nmol/l).

Results: A total of 165 subjects were enrolled at the end of winter and 142 were enrolled at the end of summer. 60% of these subjects were women (n=186) and 61% were white (n=185). 64% (n=91) of the subjects drank milk at the end of summer and 58% (n=96) at the end of winter. An average of 1.6 (± 1) glasses of milk was consumed per day. There was no statistical significance between age groups and the percentage of the population who drank milk. 40% of the subjects (n=123) reported that they took a multivitamin during the summer and winter. There was also no significant difference in multivitamin use between the age groups.

This study determined that vitamin D insufficiency was more common at the end of winter with a value of 30% (n=49) compared to the end of summer with a value of 11% (n=16). Seasonal variations were most significant in subjects 18-29 years of age (Figure 2). Serum 25-hydroxyvitamin concentrations increased 30% (28 ± 10 ng/mL to 36 ± 10 ng/mL) from the end of winter to the end of summer in the 18-29 year-olds, 3% (31 ± 10 ng/mL to 32 ± 10 ng/mL) in

subjects 30-39, 12% (27 ± 10 ng/mL to 30 ± 10 ng/mL) in the age range 40-49 and 5% (35 ± 10 ng/mL to 37 ± 10 ng/mL) in subjects greater than 50 years old. Vitamin D insufficiency was more prevalent in all age groups during the winter and the oldest group was least likely to be vitamin D insufficient during the summer and winter (Figure 3). Subjects who took a multivitamin had 30% higher (37 ng/mL vs. 29 ng/mL) serum 25(OH)D concentration than those who did not take a multivitamin. There was no difference in serum 25(OH)D levels between the patients who drank milk and those who did not drink milk.

Discussion: It was observed that 36% of young adults ages 18-29 were vitamin D deficient at the end of winter with no other age group exhibiting these same results. Dietary intake of milk was not associated with higher levels of 25(OH)D but daily intake of a multivitamin containing 400 IU of vitamin D was associated with higher 25(OH)D levels. The high prevalence of vitamin D deficiency in young adults may be explained by lower consumption of foods containing vitamin D like fortified cereals and oily fishes. Most of the subjects in the younger age group that demonstrated vitamin D deficiency were students who were most likely indoors during the daylight hours in the fall and spring and outdoors during their summer vacation. This might explain the difference in 25(OH)D levels seen during winter and summer in this particular group. The sunlight, during the winter, is also incapable of producing vitamin D₃ at latitude 42° N (where Boston is located).

Validity: This was an observational study and used proper statistical analysis. An observational study is commonly used for prognosis, aetiology, and incidence/prevalence studies. Usually in an observational study the authors also indicate whether it was case series, case control, prospective, or retrospective cohort study. The type of observational study was not identified in the methods. One positive aspect of the study was that the vitamin D levels were

measured in both summer and winter over the course of the year. Researchers also looked at dietary history and correlating PTH values which are key components when analyzing vitamin D deficiency and insufficiency. The statistical methods were appropriate because they used a Student t-test to compare mean vitamin D levels and PTH levels between groups. A chi-squared test was utilized to calculate differences in proportion of vitamin D deficiency. These two tests are commonly used during observational studies. The significant problem with this study was that the sample size was very small (n=150) and that the subjects were volunteers. There was also no randomization in regards to determining the study population and there is always some bias when only volunteers are used.

“Vitamin D status in apparently healthy adults in Kashmir Valley of Indian subcontinent”

by Zargar et al. in *Postgrad Medical Journal*. 2007; 83: 713-716.¹²

Purpose: Vitamin D deficiency has become prevalent all over the world and there is little evidence about the population in Kashmir valley. This study's goal was to assess the prevalence of vitamin D deficiency in healthy volunteers in Kashmir Valley.

Methods: The Kashmir Valley is located at an altitude of 1574-525 feet above sea level at latitude 32° 20'-34° 50' N and longitude 73° 45'-75° 35'E in the Northern mountains of India. 150 healthy volunteers ranging from 18-40 years of age who resided in the Kashmir Valley for at least five years were approached and screened for eligibility. The subjects were drawn from five groups: medical professionals, employed, farmers, household and students. Those subjects with liver, kidney or gastrointestinal disease, and pregnant or lactating women were all excluded. Participants taking vitamin and mineral supplements or drugs that affect bone metabolism were

also excluded. A detailed history was taken from these subjects focusing on dietary habits, body area exposed to sun, and hours per week of exposure to sunlight. Each subject's nutritional status was also assessed estimating composition of diet in terms total energy, carbohydrate, protein, fat, and calcium intake by using a food frequency questionnaire. Sun light exposure was determined from average daily duration of exposure to sun and percentage of body surface area exposed. The average duration of cloud free sunshine during 2003 in the Kashmir Valley was 4.4 h/day in winter months (October to March) and 6.5 h/day in summer (April to September).

Results: 92 subjects (64 male and 28 non-pregnant females) ranging from 18-40 with a mean age of 28.15. Overall 76 (83%) of the studied subjects had vitamin D deficiency, defined as a serum 25-hydrovitamin D level < 50 nmol/l (20 ng/mL). 76.6% of males (49 of 64) and 94.4% (27 of 28) of females were vitamin D deficient. Mild [serum 25 (OH) D concentration < 50 nmol/l] vitamin D deficiency was seen in 25% of the population. Moderate (12.5-25 nmol/l) vitamin D deficiency was seen in 33% of the study sample and severe (< 12.5 nmol/l) vitamin D deficiency was seen in 25% of the population. Mean daily calcium intake in subjects with vitamin D deficiency was significantly lower than those subjects without deficiency. Age and occupation relationship to vitamin D status is displayed in Table 2.

Discussion: In the Kashmir Valley it was determined that 83% of their population (n=150) was vitamin D deficient. A large portion of the subjects in this study had an adequate amount of sun exposure but were still vitamin D deficient. In many other studies it has been concluded that increasing age is associated with vitamin D deficiency.⁶ In this study there was no effect of age on the prevalence of vitamin D deficiency.

All but one of the women in the study were vitamin D deficient with significantly less sun exposure and decreased body area exposure than the males of the study. The cultural

practices of those in India usually require the women to cover their face and body. This practice might explain the prevalence of vitamin D deficiency. Many women also hold indoor jobs and perform household work indoors where they do not receive adequate sun exposure. The diet of most people in the Kashmir valley consist of predominantly of rice based diet where meat is consumed 2-3 times per week. Fish and milk products are only consumed occasionally and use of vitamin D fortified foods in the Kashmir valley is negligible. All of the previous reasons can help explain the high prevalence of vitamin D deficiency in this Kashmir Valley community.

Validity: This was also an observational study and the limitations were stated by the authors. Like the previous article the type of observational study was not stated in the methods. A two-tailed p value was used for calculating statistical significance and logistic regression was used to compare factors affecting the prevalence of vitamin D. Logistic regressions are another common and appropriate statistic used for comparison. The problem with this study was that it had a relatively small sample size (n=150) and subjects were not able to be studied in both summer and winter. PTH levels were also not available. The study did, however, look at direct exposure to sunlight and calcium intake, which are both important determinants of vitamin D levels.

“Prevalence of vitamin D insufficiency in an adult normal population” by Chapuy et al. in *Osteoporosis International*. 1997; 7: 439-443.¹³

Purpose: There is an absence of data on the vitamin D status of a general French population. This studies goal was to determine the prevalence of hypovitaminosis D and its relation to serum PTH in an urban population of normal French adults.

Methods: The latitude in the French regions studied varied from 51° N to 43°N.

Participants were collected from the French SUVIMAX project. This project is an interventional epidemiological study to assess the effects of vitamins C and E, beta-carotene, minerals, and antioxidants at nutritional doses to prevent mortality to due to cardiovascular diseases, cancers, cataract, and infections. A total of 1569 adults were randomly selected containing 765 men age 45-60 and 804 women age 35-60. They were selected from 20 French cities in nine geographical regions whose latitude varies from 43° to 51° N. The subjects underwent medical examinations, biochemical tests, and answered a food frequency questionnaire. The daily hours of sunlight for each region were obtained from the Meteorological Service and were expressed as the mean value of the previous 3 months before the serum 25(OH)D was drawn.

All samples were taken between November and April when 25(OH)D values are supposed to be the lowest of the year. The statistical analysis was conducted using the *SAS statistical software package*. The relationship between PTH and 25(OH)D was studied by non-linear weighted least squares regression analysis.

Results: 1569 adults (765 men age 45-65 and 804 women age 35-60) were included in this study. Data was taken from nine cities and grouped into nine geographical regions. Vitamin D insufficiency defined as a serum 25(OH)D level ≤ 30 nmol/l (12 ng/mL) was found in 14% of the population. There was no age or sex effect on 25(OH)D values between 35 to 65 years of age but there was a significant difference in the vitamin D status between the nine regions. The lowest values were seen in the North and Center (17 ± 8 ng/ml and 18 ± 10 ng/ml) and the highest were seen in the South West (38 ± 15 ng/mL). A significant negative correlation was also found between PTH and 25(OH)D values (Figure 4). The equation shows that PTH levels

plateau at 36 pg/ml and 25(OH)D level where this plateau is reached corresponding to 78 nmol/l (31 ng/mL).

Discussion: In this French community it was noted that there was a major difference in vitamin D status. The results showed that vitamin D insufficiency occurred in 14% of the population and that it was mainly in the Northern cities. There have been several other studies performed in similar communities that demonstrate the same results. One was performed in a Swiss population during the same period (October to June) where they found that 6% of the population was vitamin D deficient (serum 25(OH)D \leq 20 nmol/l) and that 34-95% had a low concentration of vitamin D (<38 or <95 nmol/l respectively).¹⁴ In the French study it was also found that serum PTH levels were beginning to increase when serum 25(OH)D levels were equal to or lower than 78 nmol/l (31 ng/mL). Small increases in PTH levels can have potentially harmful bone effects and lead to secondary hyperparathyroidism.

Validity: Of three studies comparing adults this one had the largest sample size (n=1569) and was taken from a database where they randomized the participants used. Again, it can be classified as an observational study like the previous two. The means were compared by analysis of variance adjusting for sex and blood sampling date. A non-linear weighted least squares regression analysis was also used to study the relationship of PTH and 25(OH)D. A linear regressions analysis is appropriate for this type of comparison. They also looked at food intake, vitamin supplementation and PTH levels. Measurement of sun exposure was not discussed in their methods.

“Prevalence of vitamin D deficiency among healthy adolescents” by Gordon et al. in *Arch Pediatr Adolesc Med.* 2001; 158: 531-537.¹⁵

Purpose: The primary objective of this study was to test the hypothesis that vitamin D deficiency [25(OH)D level \leq 15 ng/ml] is prevalent among healthy adolescents. The study also wanted to determine whether a seasonal variation existed for serum 25(OH)D and PTH levels by testing the hypothesis that 25(OH)D levels would be lower and PTH levels higher in the winter. Finally, they would like to identify factors within the adolescent lifestyle that represent predictors of hypovitaminosis D.

Methods: Participants were chosen from the adolescent outpatient clinic at Children’s Hospital in Boston who were presenting for their annual physical examination between July 1, 2001 and June 30, 2003. They were classified according to season, with emphasis on patients enrolled between July and September and between January and March. Participants were excluded if they had a chronic illness and used medications that affect bone metabolism. An intake form for each patient was completed containing medical history, exercise, and general diet. Blood samples were obtained from each subject at the end of their physical. The patients were divided into 3 diagnostic categories according to serum 25(OH)D. Vitamin D insufficiency was classified as \leq 20 ng/mL (50 nmol/L), deficiency \leq 15 ng/mL (37.5 nmol/L) and severe vitamin D deficiency as 8 ng/mL (20 nmol/L).

Statistical analyses were conducted using *SPSS* for Windows and *SAS statistical software*. In the design study it was specified that 5% prevalence of vitamin D deficiency would be considered clinically significant. To assess simple bivariate associations among serum 25(OH)D level, vitamin D deficiency and predictor variables, the chi-squared statistic, the t test,

linear regression, a 1-way analysis variance, the Kruskal-Wallis test, and Pearson product moment or Spearman rank correlation were all used.

Results: The final sample was composed of 307 participants ages 11-18. Vitamin D deficiency was defined as serum 25(OH)D level ≤ 15 ng/ml and was present in 24.1% of the population. The prevalence of vitamin D deficiency of the total sample and different subgroups is displayed in Table 3. Severe vitamin D deficiency [25(OH)D level ≤ 8 ng/mL] was seen in 14 patients (4.6%) and vitamin D insufficiency [25(OH)D ≤ 20 ng/mL] was seen in 129 patients (42%). Hypovitaminosis D was also more prevalent during winter and spring compared with summer and fall (Figure 5). There was no significant difference in prevalence of vitamin D deficiency between adolescent boys and girls (26.0% vs. 20.6%, $P=0.33$). A positive correlation was noted between vitamin D deficiency and the consumption of soft drinks, fruit juice, and iced tea and an inverse correlation between vitamin D deficiency and consumption of milk and cold cereal (commonly fortified with vitamin D). There was also an inverse correlation between serum PTH and 25-hydroxyvitamin (Figure 6). 25(OH) D levels were significantly higher in multivitamin users and outdoor/total activity levels showed no relation to 25(OH)D levels.

Discussion: A high prevalence of vitamin D deficiency among an otherwise healthy adolescent population was found in this study. Dietary and seasonal issues might explain the high prevalence among healthy teenagers. Low levels of light exposure occur during the winter in Boston and likely explain the seasonal variation noted. Dietary factors may have also contributed to the high prevalence of deficiency. Milk consumption has decreased over the recent years in this population due to the increase intake of juice and soft drinks.

This study also provides evidence that vitamin D levels should be maintained at more than 15 ng/ml to maintain normal skeletal dynamics due to the inverse relationship between PTH and 25(OH)D levels. It was also found that there was an inverse correlation between body mass index and serum 25(OH)D. The study controlled for ethnicity, sex, and consumption of milk and juice but body mass index remained an independent predictor of hypovitaminosis D. There have been several studies correlating obesity with vitamin D deficiency and insufficiency. This is due to the decreased vitamin D bioavailability from cutaneous and dietary sources because of its deposition in body fat.¹⁶

Validity: This study was a cross-sectional clinic-based design where the authors addressed the limitations. Because this was a cross-sectional study, causality cannot be inferred. If a longitudinal study had been performed then it would have been able to confirm that the correlates are definite risk factors for hypovitaminosis D. It also would have determined whether vitamin D supplementation has significant beneficial health effects in adolescents. The study sample also had a large number of subgroups that are at a potentially higher risk for low vitamin D levels including: African American, Hispanic, and overweight teenagers. This sample might not be representative of all Boston adolescents because of referral bias. The positive aspects of the study were that they looked at vitamin and food intake, sun exposure, daily activity, and PTH levels. Their statistical analyses were conducted very thoroughly and many different predictor variables were taken into account and analyzed.

“Hypovitaminosis D in healthy schoolchildren” by Fuleihan et al. in *Pediatrics*. 2001; 107: 53-59.¹⁷

Purpose: The primary objective of this study was to test the hypothesis that vitamin D insufficiency is prevalent in healthy school adolescents. Another objective was to establish that insufficiency is more common in girls than boys and in schools of lower socioeconomic status (SES). Finally, they wanted to determine the impact of low vitamin D levels on biochemical indices of bone remodeling during a critical period for bone mass accretion.

Methods: Three private schools in Beirut, Lebanon at latitude 33.5° N were used for participant selection. Two schools were categorized as high SES, where the students' fees were \$5000-\$7000 and the third school was categorized as medium, with school fees of \$1500. The age group studied was 10-16 years because this is the critical period for skeletal mass accretion. Children with any medical conditions or medications known to affect skeletal metabolism were excluded. The study was implemented in two periods: the spring (March to April) and the end of summer (October) but was delayed because of logistical reasons so actually took place in the fall (November to December). All participants had their height and weight measured and answered a dietary questionnaire based on 7-day food frequency questionnaire. Vitamin D deficiency was defined as a serum 25(OH)D < 10 ng/mL and insufficiency was defined between 10-20 ng/mL.

Statistical analysis was performed using *SPSS Software Version 9.0* and *GraphPad Prism Software*. Results were expressed as mean ± standard deviation unless mentioned otherwise. Comparison of variables was performed using a 2-tailed t test. The relationship between 25(OH)D and continuous variables (age, BMI, sun exposure, calcium intake, vitamin D intake,

and Tanner stage) was evaluated using Pearson correlation coefficient. A linear multiple-regression model was used to determine the predictors for 25(OH)D levels in the spring and fall.

Results: The sample consisted of 169 white students equal in both genders ages 10-16. The proportion of children who were vitamin D deficient was higher in girls than in boys during both seasons (32% vs. 9% in spring and 7.5% vs. 0% in fall). The proportion of children with insufficiency was 42% versus 46% in the spring and 46% vs. 25.3% in the fall in boys and girls respectively. The girl participants also had less sun exposure and calcium intake than boys in both spring and fall. This study also looked at socioeconomic status and found that schools with higher SES had higher vitamin D levels than those children attending schools of middle or lower SES. Sun exposure, calcium intake, vitamin D intake, and vitamin D levels can be seen in Table 4. The significant predictors were BMI, gender, and SES in the spring [$R^2 = 0.53$ ($P \leq 0.001$)] and in the fall [$R^2 = 0.28$ ($P < 0.001$)]. When spring and fall were combined the significant predictors were gender, SES, BMI and season with an $R^2 = 0.43$ ($P < 0.001$). An inverse relationship was also noted for vitamin D levels and PTH levels.

Discussion: Vitamin D levels below 20 ng/mL were seen in 65% of the population in winter and 40% of the population in summer. Sun exposure and vitamin D intake were significant predictors of vitamin D levels along with gender, SES and BMI regardless of the season. This study was one of the first to simultaneously evaluate the impact of gender, season and SES on vitamin D levels. One reason vitamin D levels are so low in this population is that Lebanon, similar to other Middle Eastern and some European countries, does not have regulations mandating vitamin D supplementation of milk. The main source of vitamin D comes from skin synthesis in response to sun exposure. Young girls from the middle SES school also

had to observe a strict dress code where their head, arms and legs are all covered, thus limiting sun exposure.

Validity: This was an observational study and many different predictors of vitamin D deficiency and insufficiency were examined. The authors took into account sun exposure, gender, SES, BMI, Tanner staging, PTH and dietary intake. The statistical methods were also appropriate since they used a 2-tailed t test for comparison of variables between the subgroups. Nonlinear and linear multiple regression was also used to determine the predictors for 25(OH)D levels. The problem with this study was that the population was fairly small (n=169) and this could have skewed some of the findings. The participants were also not randomly selected because then there would have been a bias for higher SES schools.

“Vitamin D intake is low and hypovitaminosis D common in healthy 9-15 year old Finnish girls” by Lehtonen-Veromaa et al. in *European Journal of Clinical Nutrition*. 1999;53:746-751.¹⁸

Purpose: To investigate the daily dietary intake of vitamin D and calcium as well as compare dietary intake of vitamin D with 25(OH)D concentrations in athletic and nonathletic 9-15 year old girls during a one year follow-up.

Methods: The participants were enrolled as volunteers who were recruited from local sports clubs and schools in the city of Turku, Finland and its vicinity. The girls were considered as pursuing competitive athletics if she had participated regularly in competitive sports at a local, provincial or national level for at least one year. A subject was referred to as the control group if

she did not participate in any kind of regular or organized sport. All subjects were healthy and had no chronic illnesses that could affect growth or metabolism of calcium or vitamin D.

The subjects were studied at a baseline over an eight-week period in between February and March of 1997. Weight, height, and BMI were recorded. At the six month visit a multivitamin supplement (Optivit) containing D10ug was given to all participants. They were asked to take one tablet per day from the beginning of October for at least three months. Supplementation was stopped one month before the end of the follow-up period. Calcium supplementation was given to those who consumed less than 1000 mg/d. Questionnaires were administered to determine vitamin D intake, calcium intake, physical activity, and medical history. All travels to lower latitudes were also documented and the duration of these visits noted. Severe hypovitaminosis D was defined as serum 25(OH)D < 20 nmol/l and moderate hypovitaminosis D between 20-37.5 nmol/l. *SAS 6.12 statistical software* was used to run analyses. Comparisons of means between groups were done with a 2-sample t-test and Fishers exact tests were performed to compare proportions of athletes and the control group.

Results: 186 girls participated in the one year follow up. There were no significant differences between the groups concerning height or weight. The mean daily intake of vitamin D was similar between athletes and controls. The athletes consumed more calcium, carbohydrates, total fat and protein than the controls. 22% of the participants took vitamin D supplementation at least four times a week at baseline and no less than 93.4% at the 12 month visit. At the baseline level (February to March) the mean serum 25(OH)D concentration in all participants was 33.9 nmol/l. The participants who took vitamin D at the beginning of the study had a higher 25(OH)D level (43.3 nmol/l vs. 31.2 nmol/l $P < 0.001$) then those who did not (Table 5). The prevalence of severe hypovitaminosis D was 13.4% and of moderate hypovitaminosis D was

67.7% at baseline (February to March). At a 12 month follow up visit after three months of vitamin D supplementation 63.4% still had hypovitaminosis D and 9.1% had severe hypovitaminosis D. The prevalence of hypovitaminosis D between the baseline visit and the 12-month visit did not differ significantly in the group of participants who took 10ug/d of vitamin D supplementation for three months.

Discussion: It was determined that three months of vitamin supplementation did not significantly reduce the prevalence of hypovitaminosis D. The average dietary vitamin D intake of girls aged 12-15 in Finland had previously been reported to be 2.1 to 3.0 ug/d. Although the daily intake in this study was below the recommend daily allowance of vitamin D, 22% of the population took vitamin D supplements at least four times a week at the beginning of the study. 65% of the participants did not use vitamin D supplementation at baseline and had a mean 25(OH)D level of 32.2 nmol/l. Those taking multivitamins at the beginning of the study had a significantly higher serum 25(OH)D level (43.3 nmol/l). Given this evidence the authors recommend vitamin D supplementation should be used more widely and that peripubertal children should consume a vitamin D supplement.

Validity: This study was also an observational study and proper statistical analysis was used. Comparisons of means between groups were performed by a 2-sample t-test and comparisons of means between questionnaire and food record was done by a paired sample t-test. The authors state that one problem with this study is that the correlation between the two methods estimating dietary intake of vitamin D was statistically significant but weak. This may be due to the fact that almost all participants only consumed small amounts of vitamin D. The study sample size was also small (n=186) and consisted of volunteers. There was no randomization and considering only girls were studied a large majority of the population is

missing. One variable that was not taken into account was sun exposure. However, this study was one of few that had scheduled follow up for the participants.

DISCUSSION

As demonstrated by the results of the articles, vitamin D deficiency and insufficiency is very prevalent among adults and adolescents in various communities. Although the studies differed in sample size, population, and variables analyzed; the conclusions, for the most part, were the same. Several of the studies determined that despite an abundance of sun exposure, combined with vitamin D consumption through foods and supplementation, low levels of vitamin D existed in all of the diverse populations. Evidence shows that the prevalence of vitamin D deficiency and insufficiency is a significant and growing problem that needs to be addressed and controlled.

When discussing the prevalence of vitamin D deficiency and insufficiency it is first important to look at the causes. One of the most significant causes is reduced skin synthesis of vitamin D. This can be due to several factors including the use of sun screen, pigmented skin, and general aging. Affective skin synthesis is also dependent on the season, latitude, and time of day. Above 35° N latitude (Atlanta) little or no vitamin D₃ can be produced between November and February.⁹ Another important cause of low levels of vitamin D is decreased bioavailability. Certain individuals have malabsorption problems due to reduced fat absorption. This absorption problem can be caused by diseases like cystic fibrosis, celiac disease, Whipple's disease, Crohn's disease, bypass surgery, and medications that reduce cholesterol absorption. The obese

population also experience decreased bioavailability of vitamin D from cutaneous and dietary sources because of the tendency of the vitamin D to deposit in the adipose tissue.^{16,19}

Increased catabolism of certain types of medications also contributes to low levels of vitamin D. Medicines like anticonvulsants, glucocorticoids, HAART (AIDS treatment), and antirejection medications activate the destruction of 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D and convert it into inactive calcitroic acid.² Breast feeding also causes deficiency in infants due to the poor vitamin D content in human milk. This leads to an increased risk of vitamin D deficiency when breast milk is the sole source of nutrition.¹⁹

Many different types of diseases also contribute to low levels of vitamin D in the blood. Liver failure causes a decreased synthesis of 25(OH)D and malabsorption problems. Nephrotic syndrome results in a substantial loss of 25(OH)D to the urine. Patients with kidney disease have decreased fractional excretion of phosphorous therefore decreased serum levels of 1,25-dihydroxyvitamin D. The inability to produce adequate amounts 1,25-dihydroxyvitamin D causes hypocalcaemia, secondary hyperparathyroidism, and renal bone disease. Heritable disorders, such as rickets, reduce or eliminate renal synthesis of 1,25-dihydroxyvitamin D. Finally, acquired disorders such as tumor-induced osteomalacia, primary hyperparathyroidism, granulomatous disorders, sarcoidosis, tuberculosis and hyperthyroidism all cause decreased levels of 25(OH)D in the blood.²

Since it has been determined that the prevalence of vitamin D deficiency and insufficiency is substantially higher in a number of populations, it is important to review the effects of low levels of vitamin D on the individual. Without vitamin D it is estimated that only 10-15% of dietary calcium and about 60% of phosphorous are absorbed.² Calcium is essential

for the maintenance and function of bone formation and growth in all ages. Inadequate calcium absorption and low vitamin D status results in impaired bone mineralization and leads to bone softening diseases such as rickets, osteomalacia, and osteoporosis. Rickets is a childhood disease characterized by impeded bone growth and a deformity in the long bones. In children, low vitamin D levels can also prevent them from reaching their genetically programmed height and peak bone mass. Osteomalacia is a bone thinning disorder that occurs in adults and is characterized by bone fragility and proximal muscle weakness. These skeletal muscles have vitamin D receptors and require vitamin D for maximum function. Osteoporosis is a condition where there is reduced bone mineral density accompanied by increased bone fragility. Because all of these conditions weaken the bones, the risk for fractures is also greatly increased.^{10, 13,12,20,}

^{21,22}

Along with the bone and muscle effects vitamin D has on the body there are also other non-skeletal functions of vitamin D. Brain, prostate, breast, colon tissues and immune cells all possess a vitamin D receptor and respond to 1,25-dihydroxyvitamin D (the active form of vitamin D). Directly or indirectly, 1,25-dihydroxyvitamin D controls more than 200 genes. This includes genes responsible for the regulation of cellular proliferation, differentiation, apoptosis and angiogenesis. Because vitamin D has these functions, many studies have been done on the role of vitamin D in the prevention of common cancers, autoimmune diseases and heart disease.

^{3,7,8,13,23}

Prospective and retrospective epidemiologic studies have indicated that levels of 25(OH)D that are below 20 ng/mL are associated with a 30-50% increased risk of developing colon, prostate, breast and ovarian cancer. This also contributes to higher mortality rates from these cancers.² Pooled data from 980 women showed that the highest vitamin D intake as

compared with the lowest, correlated with a 50% lower risk of breast cancer. Vitamin D and its metabolites reduce the incidences of many types of cancer by inhibiting tumor angiogenesis, stimulating mutual adherence of cells, and enhancing intracellular communication through gap junctions. By doing this they are thereby strengthening the inhibition of proliferation that results from tight physical contact with adjacent cells within a tissue and reducing the potential for malignant cells to survive.²⁵

There is also reasonable evidence linking vitamin D status as a potential environmental factor affecting autoimmune disease prevalence. Data shows that there is a link between low levels of vitamin D and insulin-dependent diabetes mellitus, multiple sclerosis, inflammatory bowel disease and rheumatoid arthritis.^{5,7,10,15} Autoimmunity is driven by T-helper cells which attack various self-tissues in the body. It is clear that environmental and genetic factors affect diseases prevalence. But the fact that vitamin D has been implicated as a factor in several different autoimmune diseases suggests that vitamin D plays a role in the development of self-tolerance. The vitamin D hormone (1,25-dihydroxyvitamin D3) regulates T-helper cells and dendritic function while inducing regulatory T-cell function. The net result is a decrease in the T-helper cell driven autoimmune response and a decreased severity of symptoms.²⁴

Epidemiological research shows that living at higher latitudes increases the risk of hypertension and cardiovascular disease. Individuals who live at higher latitudes are at a higher risk for vitamin D deficiency. A study was conducted in which high altitude patients with hypertension were exposed to ultraviolet B radiation three times a week for three months. The outcome was that the 25(OH)D levels increased by 180% and both systolic and diastolic blood pressure reduced by 6 mm Hg. Along with high blood pressure, vitamin D deficiency has been linked to an increased incidence of schizophrenia and depression. Maintaining vitamin D

sufficiency in utero and early on in one's life is important for brain development as well as for preservation of mental function later in life.²

The importance of adequate levels of vitamin D is illustrated by the numerous physiological effects that deficiency and insufficiency have on the body. A sufficient amount of vitamin D is vital for all individuals of all ages. To obtain adequate levels of vitamin D, humans can either expose themselves to a reasonable amount of UVB or ingest a vitamin supplement. Throughout the United States the estimated daily solar exposure to maintain a serum 25(OH)D level of 30 ng/mL is 15 minutes in summer and 20 minutes in early fall or late spring. The exposure must occur between 11:00 AM and 2:00 PM under clear skies. Exposure of the arms, shoulders, and back is needed to obtain the proper amount. Between November and March, north of 37° latitude in the Northeastern and mid-Atlantic regions, no amount of solar exposure is sufficient. In the Northwest and most other regions, some UVB is available during winter, although low ambient temperatures limit duration and area of exposure.²⁵

If inadequate sun exposure is common, vitamin supplementation is recommended. The Institute of Medicine recommends the adequate daily intake of vitamin D for adults up to 50 years of age is 200 IU, 51-70 years is 400 IU, and individuals older than 71 should consume 600 IU.^{2,4} The American Academy of Pediatrics has recently increased the recommended dose for infants, children and adolescents from 200 IU daily to 400 IU daily. This change was instituted after the review of numerous clinical trials stating that 400 IU not only prevents rickets but actually treats the disease.²⁶

This review successfully identified the prevalence of vitamin D deficiency and insufficiency in numerous adult and adolescent populations but the limitations need to be

considered. One of the major limitations of this study was that it was a review and not a clinical trial, observational study, or meta-analysis. The articles were reviewed and discussed by one person and conclusions were made based on available literature. No opinions, however, were included in this review. It is also important to note that all of the articles discussed in this review were observational studies. An observational study is the most common method when examining the prevalence of a certain condition. However, it would have been beneficial if a randomized clinical trial or meta-analysis could have been included.

Another limitation of the study is that a pertinent article may have been overlooked during the literature search. This risk was reduced through the utilization of several different databases to elicit articles. An inquiry was also made to the Oregon Public Health Division epidemiologic department to determine what other databases would have been beneficial. The epidemiologist contacted gave insightful information regarding different departments and sites that would have had pertinent information for the review. When further studies are conducted on the prevalence of vitamin D deficiency and insufficiency the sites and information given by the epidemiologist will be extremely helpful. As evidence of this review, vitamin D deficiency and insufficiency has become an increasing problem in a variety of populations. This significant condition must be studied more thoroughly and controlled in order to prevent the lasting medical effects.

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Table 1. Dietary, Supplemental, and Pharmaceutical Sources of Vitamins D2 and D3. ²	
Source Vitamin D Content	
Natural sources	
Salmon	
Fresh, wild (3.5 oz)	About 600–1000 IU of vitamin D3
Fresh, farmed (3.5 oz)	About 100–250 IU of vitamin D3 or D2
Canned (3.5 oz)	About 300–600 IU of vitamin D3
Sardines, canned (3.5 oz)	About 300 IU of vitamin D3
Mackerel, canned (3.5 oz)	About 250 IU of vitamin D3
Tuna, canned (3.6 oz)	About 230 IU of vitamin D3
Cod liver oil (1 tsp)	About 400–1000 IU of vitamin D3
Shiitake mushrooms	
Fresh (3.5 oz)	About 100 IU of vitamin D2
Sun-dried (3.5 oz)	About 1600 IU of vitamin D2
Egg yolk About 20 IU of vitamin D3 or D2	
Exposure to sunlight, ultraviolet B radiation (0.5 minimal erythral dose)†About 3000 IU of vitamin D3	
Fortified foods	
Fortified milk	About 100 IU/8 oz, usually vitamin D3
Fortified orange juice	About 100 IU/8 oz vitamin D3
Infant formulas	About 100 IU/8 oz vitamin D3
Fortified yogurts	About 100 IU/8 oz, usually vitamin D3
Fortified butter	About 50 IU/3.5 oz, usually vitamin D3
Fortified margarine	About 430 IU/3.5 oz, usually vitamin D3
Fortified cheeses	About 100 IU/3 oz, usually vitamin D3
Fortified breakfast cereals	About 100 IU/serving, usually vitamin D3
Supplements	
Prescription	
Vitamin D2 (ergocalciferol)	50,000 IU/capsule
Drisdol (vitamin D2) liquid supplements	8000 IU/ml
Over the counter	
Multivitamin	400 IU vitamin D, D2, or D3‡
Vitamin D3	400, 800, 1000, and 2000 IU

Table 2. Age and occupation in relation to vitamin D status. ¹²

	Vitamin D deficient (n = 76) (%)	Vitamin D sufficient (n = 16) (%)	Total
Age group (years)			
20-24	15 (93.8)	1 (6.3)	16
25-29	36 (81.8)	8 (18.2)	44
30-34	17 (81.0)	4 (19.0)	21
35-40	8 (72.7)	3 (27.3)	11
Occupation			
Farmer	12 (70.6)	5 (29.4)	17
Government employee	16 (69.6)	7 (30.4)	23
Household	15 (100.0)	–	15
Medical professional	21 (91.3)	2 (8.7)	23
Student	12 (85.7)	2 (14.3)	14

Table 3. Prevalence of vitamin D deficiency in the total sample and in different subgroups of an adolescent population.¹⁵

Variable	Total Subjects	No. (%) of Subjects With Vitamin D Deficiency*	OR (95% CI)†
All	307	74 (24.1)	NA
All, standardized	307	31 (10.1)‡	NA
Ethnicity			
African American	142	51 (35.9)	8.59 (2.53-29.20)
Hispanic	78	17 (21.8)	4.27 (1.18-15.50)
Asian	6	1 (16.7)	3.07 (0.26-35.70)
White	49	3 (6.1)	Reference
Sex			
Female	200	52 (26.0)	1.36 (0.77-2.39)
Male	107	22 (20.6)	Reference
Season			
Fall	89	15 (16.9)	1.47 (0.65-3.28)
Winter	66	26 (39.4)	4.70 (2.19-10.10)
Spring	45	20 (44.4)	5.78 (2.52-13.30)
Summer	107	13 (12.1)	Reference
Multivitamin use			
Yes	37	3 (8.1)	0.24 (0.07-0.82)
No	267	71 (26.6)	Reference
Body mass index	NA	NA	1.04 (0.99-1.09)

Abbreviations: CI, confidence interval; NA, data not applicable; OR, odds ratio.

*Defined as a 25-hydroxyvitamin D level of 15 ng/mL or less (≤ 37.5 nmol/L).

†From simple (unadjusted) logistic regression.

‡Projected to a hypothetical sample composed of equal numbers of male and female subjects, an equal distribution across 4 seasons, and the ethnic distribution of US 15-year-old adolescents.

Table 4. Vitamin D levels, sun exposure and dietary calcium and Vitamin D intake in adolescents. ¹⁷

Variable	Spring			P-value	Fall			P-value
	All	Boys	Girls		All	Boys	Girls	
25-OHD ng/mL	17 ± 18	19 ± 7	15 ± 5	<0.001	22 ± 7	24 ± 62	19 ± 7	<0.001
25-OHD <10 ng/mL	21%	9%	32%	0.006	4%	0%	7.5%	0.2
25-OHD 10-20 ng/mL	44%	46%	42%	0.006	36%	25%	46%	0.2
Sun min/d	57 ± 48	65 ± 51	48 ± 44	0.03	87 ± 62	10 ± 52	75 ± 67	0.007
Calcium mg/d	608 ± 543	740 ± 644	487 ± 395	0.002	710 ± 382	787 ± 393	645 ± 362	0.02
		Not	available		150 ± 159	150 ± 157	150 ± 161	NS

Table 5. Mean serum 25-hydroxyvitamin D concentration during 1-year follow-up in adolescent girls.¹⁸

<i>Follow-up visit</i>	<i>Whole group</i>		<i>Participants not taking supplementation at baseline</i>		<i>Participants taking supplementation at least 4 times a week at baseline</i>	
	<i>n</i>	<i>S-25(OH)D nmol/l</i>	<i>n</i>	<i>S-25(OH)D nmol/l</i>	<i>n</i>	<i>S-25(OH)D nmol/l</i>
At baseline (February-March)	186	33.9 (13.9)	144	31.2 (12.2)	42	43.3 (15.2) ^{a***}
At 6 months (August-September)	187	62.9 (15.0) ^{b,c***}	145	62.7 (14.8) ^{b,c***}	42	63.8 (15.6) ^{b,c***}
At 12 months (February-March)	186	33.7 (11.4)	145	32.9 (11.2)	41	36.6 (11.7) ^{d*}

^aS-25-OH-D at baseline in the supplementation group differ from without supplementation group.

^bS-25-OH-D at the 6 months differ from baseline.

^cS-25-OH-D at the 6 months differ from 12 months.

^dS-25-OH-D at the 12 months differ from at baseline.

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

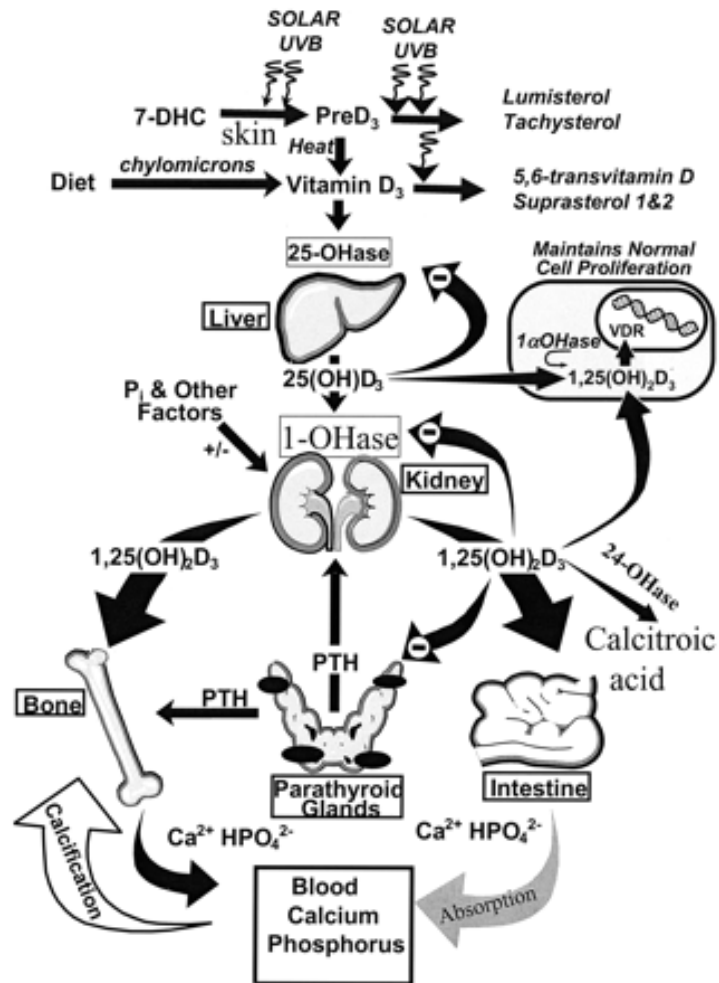


Figure 1. Photosynthesis of vitamin D₃ and the metabolism of vitamin D₃ to 25(OH)D₃ and 1,25(OH)₂D₃. Once formed, 1,25(OH)₂D₃ carries out the biologic functions of vitamin D₃ on the intestine and bone. Parathyroid hormone (PTH) promotes the synthesis of 1,25(OH)₂D₃, which, in turn, stimulates intestinal calcium transport, bone calcium mobilization and regulates the synthesis of PTH by negative feedback.³

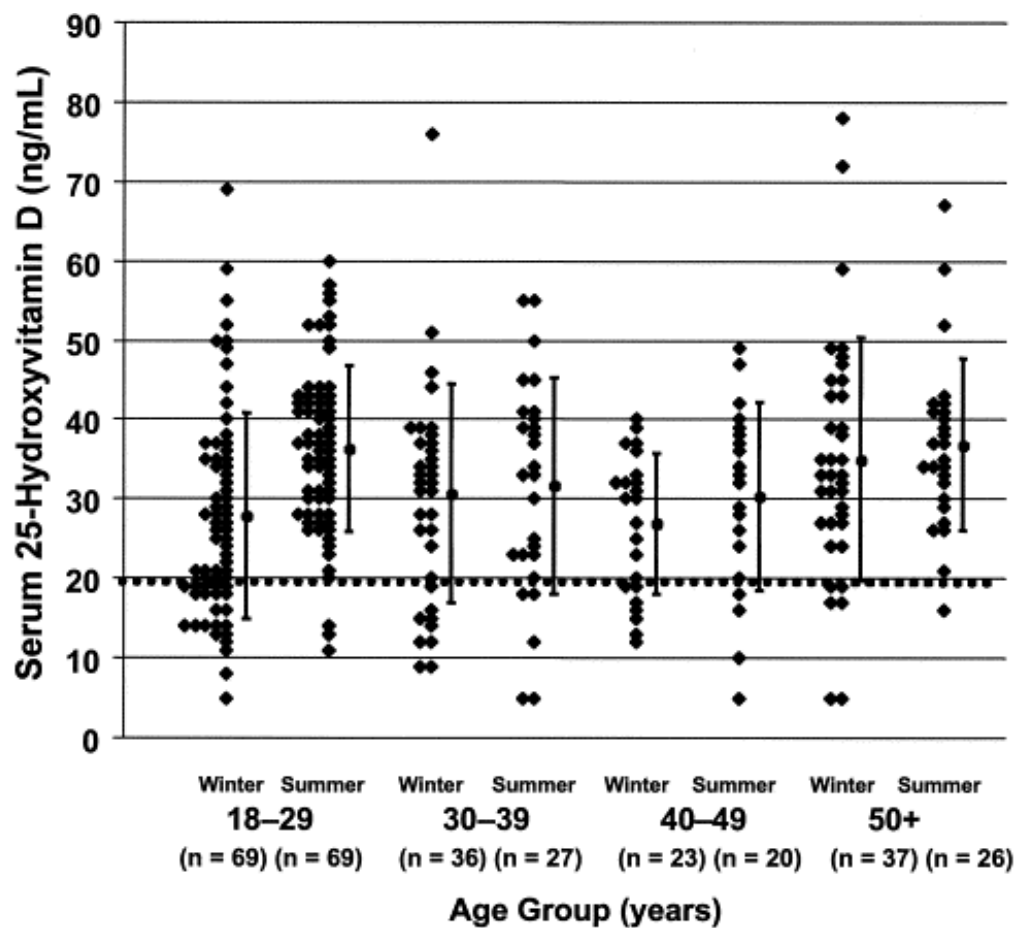


Figure 2. Seasonal variation in 25-hydroxyvitamin D levels by different age group. Means are represented with error bars showing the SD. The dashed horizontal line represents the minimum level of 25-hydroxyvitamin D considered to be vitamin D sufficient.⁸

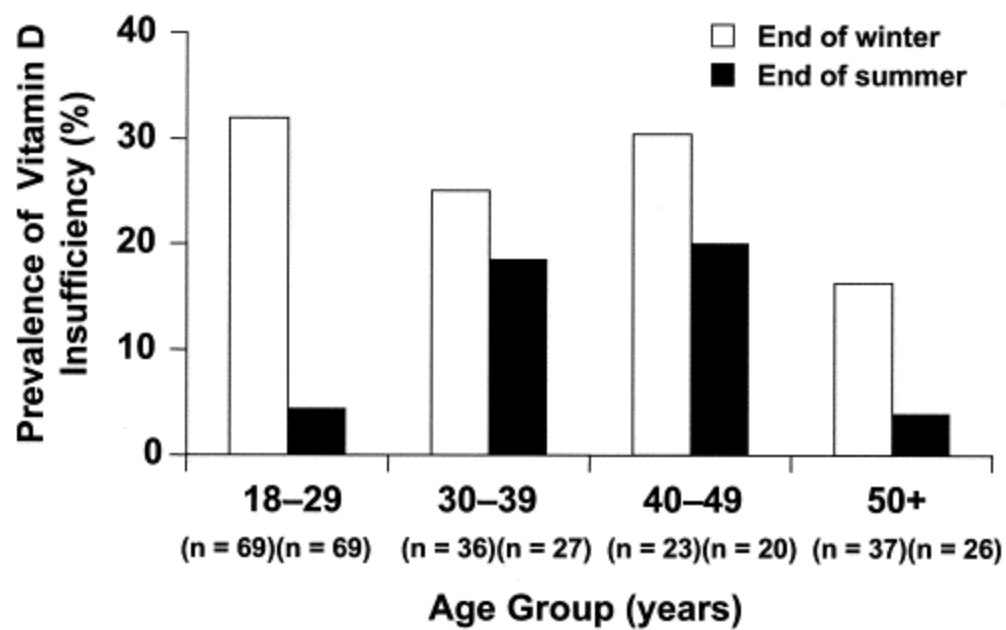


Figure 3. Percentage of subjects separated into four age groups who were vitamin D deficient (25-hydroxyvitamin D level ≤ 20 ng/mL).⁸

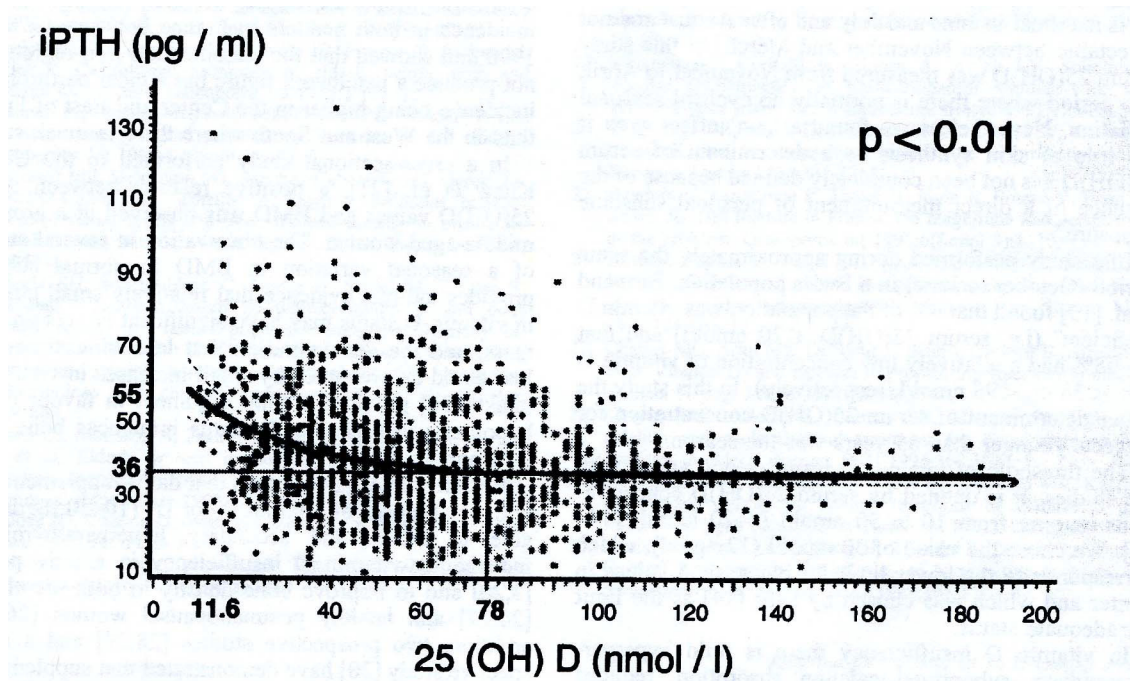


Figure 4. Relationship between serum PTH and 25-hydroxyvitamin D values for the entire studied containing adults.¹³

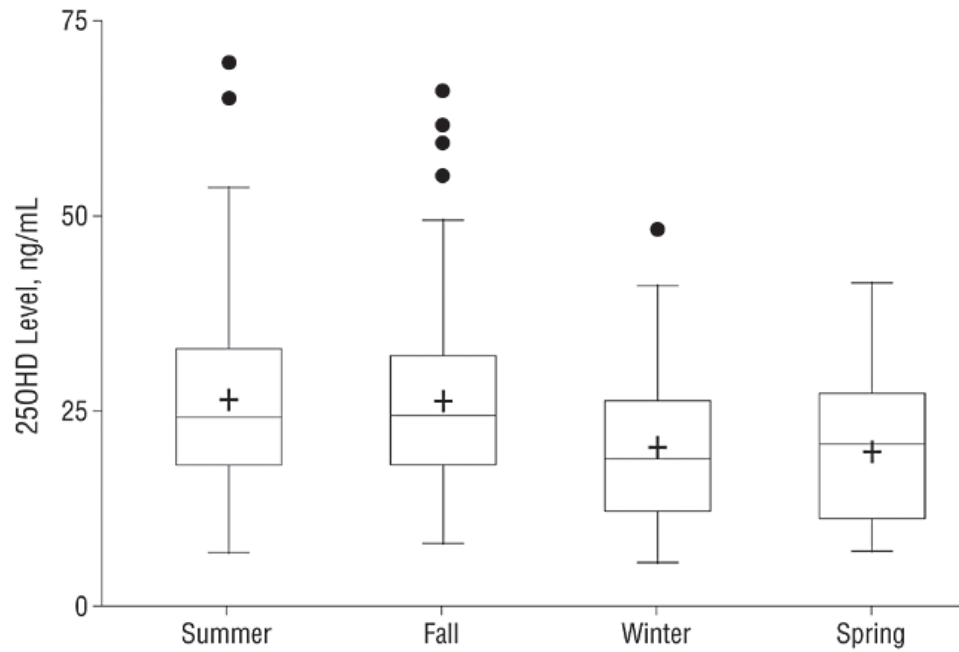


Figure 5. Box plot of seasonal variation in serum 25(OH)D in an adolescent population. The center line indicates the median; the + is the mean; the top and bottom of the box are quartile boundaries; the vertical bars are the minimum and maximum values within 1.5 times the interquartile range of the quartile boundary; and the circles are the extreme values.¹⁵

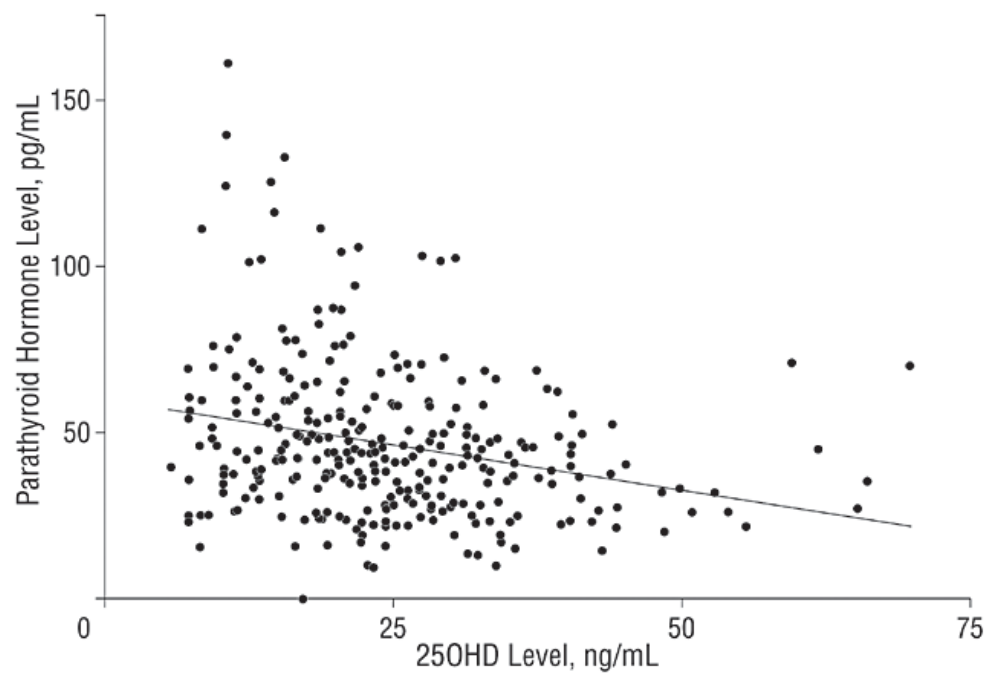


Figure 6. Relationship between serum 25-hydroxyvitamin D and PTH levels in an adolescent population.¹⁵